Beta-cell Deterioration Determines the Onset and Rate of Progression of Secondary Dietary Failure in Type 2 Diabetes Mellitus: the 10-year Follow-up of the Belfast Diet Study

J. Levy[1], A.B. Atkinson[2], P.M. Bell[2], D.R. McCance[2], D.R. Hadden*[2]

[1]*Diabetes Research Laboratories, Radcliffe Infirmary, Oxford, UK*
[2]*Sir George E. Clark Metabolic Unit, Royal Victoria Hospital, Belfast, UK*

Secondary failure of plasma glucose control following initial successful response to diet therapy may be due to dietary indiscretion, or to progression of the intrinsic diabetic condition. We report a 10-year prospective natural history study of 432 newly diagnosed diabetic patients aged 40–69 years undertaken to assess the effect of intensive dietary management, where patients were transferred to insulin, or oral hypoglycaemic therapy (tolbutamide, metformin) by predetermined criteria of weight and plasma glucose. Secondary failure to diet therapy occurred in 41 patients in years 2–4, 67 patients in years 5–7, and 51 patients in years 8–10; 173 patients remained on diet alone until death or the end of the study. Continuation on diet alone was associated with a lower ongoing fasting plasma glucose, greater beta-cell function assessed by an oral glucose tolerance test at 6 months, and increasing age. The rate of rise of fasting plasma glucose was inversely related to the duration of successful dietary therapy, but mean weight remained constant in all groups while on diet alone. The ongoing fall in beta-cell function assessed by HOMA modelling closely mirrored the progressive rise in fasting plasma glucose: there was no change in mean insulin sensitivity in any of the groups.

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Introduction

A natural history study is designed to follow the progression of a long-term degenerative disorder for which there may not be an effective remedy. The gradual onset of complications, or ultimate mortality, can be related both to baseline characteristics and to the effectiveness of control of the pathological process with the passage of time. Diabetes mellitus is a suitable disease to study in this way, with plasma glucose control being the obvious characteristic to measure: a central feature of Type 2 diabetes is the progression of the metabolic abnormality with rising glucose levels and the need to escalate therapeutic intervention.

Macrovascular disease is independently related to increasing fasting plasma glucose.[1] The investigation of this progression and the factors that determine it is hampered by the heterogeneity of the disease and the introduction of drug therapies which alter the metabolic processes. The Belfast Diet Study,[2–5] by following a large cohort of patients for 10 years in a clinical setting, maintaining an active dietary management throughout this period, and instituting drug therapy according to well-defined and uniform criteria, provides a suitable setting for such an investigation. Model assessment using fasting glucose and insulin measurements allows calculation of ongoing indices of beta-cell function and insulin sensitivity, and these factors may be more related to long-term problems. A preliminary analysis of the first phase of the study identified declining pancreatic beta-cell function as the principal factor associated with the rise in glucose concentrations. This paper extends this analysis to the full data set by examining the examination of the effect of beta-cell failure and other factors on the rate of metabolic progression and the failure of dietary therapy.

*Correspondence to: Professor D.R. Hadden, Sir George E. Clark Metabolic Unit, Royal Victoria Hospital, Belfast BT12 6BA, UK

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Subjects and Methods

The Belfast Diet Study

The Belfast Diet Study was started in 1972 with the aim of studying the effects of intensive dietary management of diabetes presenting aged 40–69 years, on blood glucose control, morbidity and mortality.[2,3] A secondary aim was to follow the natural history of diabetic patients in the setting of a hospital diabetic clinic. Shortly before, the University Group Diabetes Program (UGDP) had suggested that addition of tolbutamide or phenformin to diet therapy was of no benefit to cardiovascular mortality.[4] The Belfast study therefore concentrated on intensive dietary management, with regular frequent dietary and clinical reviews. In addition to clinical review, patients had fasting blood samples taken for plasma glucose, insulin, and lipids every 3 months for the first 6 years of the study, then annually until the final 10-year review, and had oral glucose tolerance tests at 0 and 6 months and at 6 years. Treatment guidelines were uniform for the duration of the follow-up period, with thresholds for the initiation of additional oral hypoglycaemic or insulin therapy somewhat higher than would be accepted today. The long follow-up period, emphasis on dietary management, uniform treatment guidelines and fasting biochemical measurements make it particularly suitable for studying the natural history and underlying control mechanisms of the hyperglycaemia of diabetes.

Interim analyses have been published of the first 6 years of the first phase of the study, which recruited 223 patients between 1972 and 1976. These demonstrated a fall in plasma glucose and weight in the first few months of dietary management, with approximately 80 % of patients remaining on diet alone for the first 6 years following diagnosis.[5] In these patients a progressive rise in fasting plasma glucose was seen, associated with a progressive fall in an index of pancreatic beta-cell function, but there was no change in either mean weight or insulin sensitivity.[6]

The present paper incorporates the results of the completed study, in which 432 patients were followed until death or for 10 completed years after diagnosis. Mortality and morbidity data have been reported elsewhere.[1] This analysis concentrates on the factors determining the deterioration of glycaemic control. Compared with the interim analyses, the larger numbers and the longer duration of follow-up allow the examination of the progression of hyperglycaemia and associated underlying physiological variables, not only in patients remaining on diet therapy alone, but also in those who received oral hypoglycaemics or insulin treatment during the course of the study.

Study Protocol

Newly diagnosed diabetic patients aged 40–69 were referred by their family doctors to the Royal Victoria

Table 1. Baseline and 6-month characteristics of four groups identified by the time of failure of dietary therapy as indicated by the critria in the text

Diet therapy failure	Group 1 2nd–4th year		Group 2 5th–7th year		Group 3 8th–10th year		Group 4 none after 10 years	
Group characteristics								
Number of subjects	41		67		51		173	
Sex (M/F)	23:18		29:38		29:27		102:66	
Age at diagnosis (yr)	54 (7)		54 (7)		56 (8)		58 (7)[a d]	
	Diagnosis	6 months	Diagnosis	6 months	Diagnosis	6 months	Diagnosis	6 months
Initial conditions								
Per cent average weight (%)	116 (19)	111 (19)[g]	118 (23)	111 (21)[g]	121 (22)	110 (20)[g]	120 (21)	108 (17)[g]
Fasting plasma glucose (mmol l^{-1})	14.2 (3.8)	10.5 (3.5)[g]	12.9 (3.5)	8.7 (2.2)[g a]	12.8 (4.0)	8.7 (2.3)[g a]	11.3 (3.9)[a d f]	7.5 (2.3)[g a c f]
Fasting plasma insulin (mU l^{-1})	8.4 (4.0–18.0)	6.7 (3.2–14.4)	9.5 (5.6–16.1)	10.1 (4.5–22.5)	9.9 (5.1–19.3)	8.0 (3.7–17.1)	10.8 (5.7–20.4)	8.3 (3.7–18.5)
Beta-cell function (OGTT 30′ $\Delta\|/\Delta G$) (mU mmol l^{-1})	2.1 (3.8)	2.0 (2.9)	1.9 (2.4)	3.2 (6.6)	1.9 (2.7)	9.5 (26.0)[h]	3.1 (3.9)	5.6 (5.8)[g]
HOMA % β (%) (beta-cell function)	18 (8–43)	29 (14–63)[h]	23 (13–42)	50[g a] (28–90)	26 (12–58)[b]	43 (20–94)[g b]	34 (16–74)[a c f]	61 (30–124)[g a f]
HOMA % S (%) (insulin sensitivity)	34 (17–71)	47 (22–100)	31 (18–53)	33 (15–73)	30 (16–58)	42 (20–86)[i]	29 (15–55)	42 (19–95)[g]

Significant differences: (a) between groups at the same time points: vs group 1: [a], $p < 0.01$; [b], $p < 0.05$ vs group 2: [c], $p < 0.01$; [d], $p < 0.05$ vs group 3: [e], $p < 0.01$; [f], $p < 0.05$; (b) within groups, from diagnosis to 6 months: from diagnosis: [g], $p < 0.001$; [h], $p < 0.01$; [i], $p < 0.05$.
Significant change from 0 to 6 months: 1: $p < 0.05$; 2: $p < 0.01$; 3: $p < 0.001$.
The age, per cent average weight, and fasting plasma glucose are expressed as mean (standard deviation). The fasting plasma insulin, beta-cell function (OGTT), HOMA % B and HOMA % S are expressed as geometric mean and 1 standard deviation range (anti-logs of mean ± SD of logs).

Hospital diabetes clinic in Belfast between 1972 and 1980 if they had symptoms related to hyperglycaemia with random venous plasma glucose greater than 10 mmol l^{-1} or if they were asymptomatic but had an abnormal oral glucose tolerance test with at least one plasma glucose concentration greater than 18 mmol l^{-1}. Patients with lesser degrees of impaired glucose tolerance were excluded. An energy restricted low sucrose diet, containing approximately 42 % carbohydrate, 20 % protein, and 38 % fat with 13 g fibre per day was prescribed, and adapted individually with the aim of attaining the average body weight for sex, height, and age.[7,8] Patients were reviewed monthly for 6 months, 3 monthly until 72 months, then annually until 120 months. At each review, after overnight fasting for 14 hours, patients were weighed and had blood taken for measurement of plasma glucose, serum insulin, and lipid concentrations. At presentation, 6 months, and 72 months all patients on diet or oral hyperglycaemic agents had a 50 g oral glucose tolerance test, with measurement of plasma glucose and serum insulin at 0, 15, 30, 60, and 120 min.

The criteria for change from diet management were as follows:

1. Persistent weight loss below the average weight with a fasting plasma glucose greater than 15.0 mmol l^{-1}: this was taken as indication for insulin treatment even in the absence of other symptoms; change of treatment to insulin took place at any review after diagnosis.
2. Symptomatic or asymptomatic patients at or above average weight, but with fasting plasma glucose persistently greater than 11 mmol l^{-1} were randomized to either tolbutamide 500 mg or metformin 500 mg twice daily.

Before a patient was considered for oral hypoglycaemic treatment, a special check was made on their dietary adherence and such patients were usually admitted to

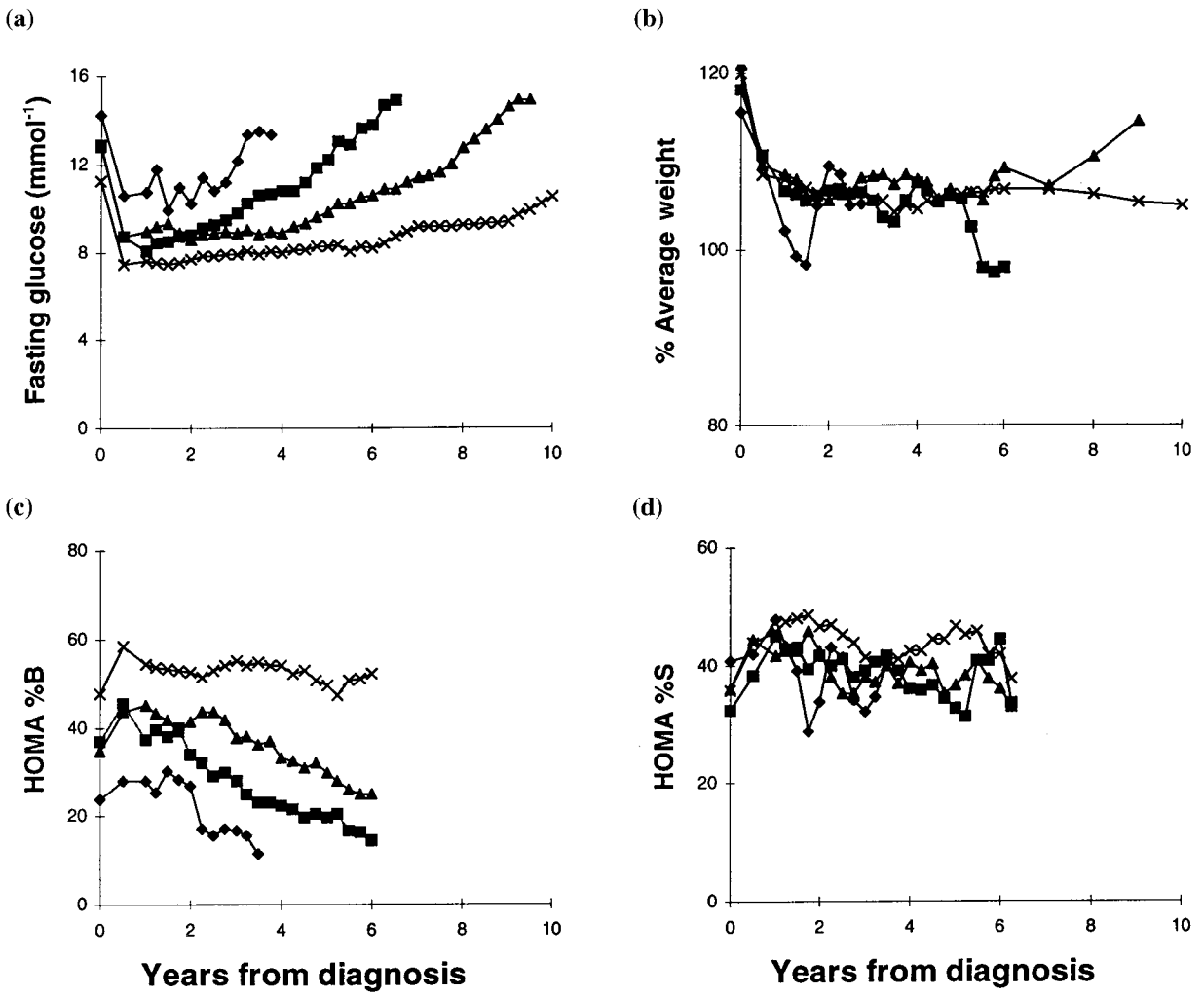

Figure 1. (a) Fasting plasma glucose; (b) average weight centile; (c) beta cell function (HOMA % B): (d) insulin sensitivity (HOMA % S) at diagnosis and at 3-monthly intervals subsequent to the 6-month review. Each graph shows four trajectories representing those patients who required additional treatment with either oral hypoglycaemic therapy or insulin during years 2–4 (◆), 5–7 (■), 8–10 (▲), and those who remained on diet only for the full 10-year review (x). Subjects were synchronized by the date of onset of additional treatment rather than by date of diagnosis

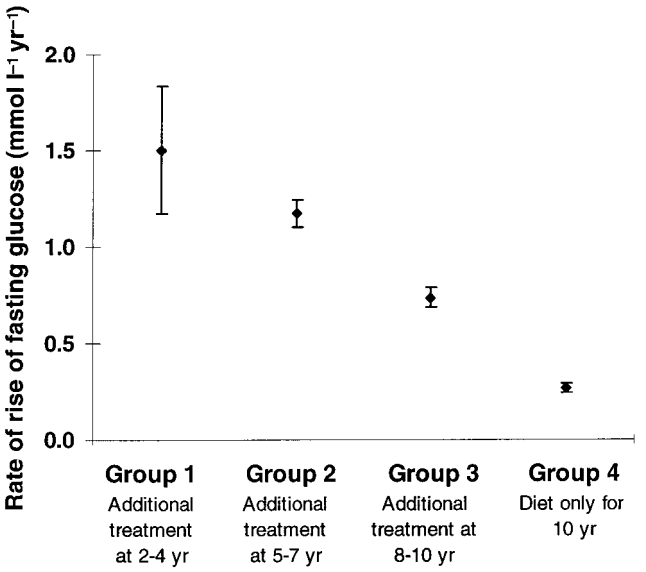

Figure 2. Mean (± SD) rates of rise of fasting plasma glucose while on diet only for the groups of diabetic patients managed on diet only up to the date of adding additional therapy (group 1 at 2–4 years, group 2 at 5–7 years, group 3 at 8–10 years), or for the whole 10-year study (group 4)

the metabolic ward for confirmation that even on a strictly supervised diet adequate control could not be achieved; change of treatment to oral hypoglycaemic therapy was only started after 6 months, but subsequently occurred at any review.[9]

Assays

During the first year of the study, whole blood glucose was measured by Technicon Auto Analyser AAI method and adjusted to plasma glucose as previously described.[5] Subsequently, plasma glucose was measured by the Technicon Auto Analyser AAII method, until 1979, when it was replaced by the Boehringer GOD PAP technique. Plasma insulin was measured by radioimmunoassay throughout.[5]

Calculations and Statistics

Beta-cell function and insulin sensitivity were assessed from fasting plasma glucose and insulin concentrations using Homeostasis Model Assessment (HOMA) analysis, using a physiologically structured computer model of the glucose and insulin homeostatic feedback mechanism to derive measures of beta-cell function (% B) and insulin sensitivity (% S). These measures are expressed as percentages of values in a lean young non-diabetic reference population. These measures have been shown to perform comparably with those derived from standard physiological tests.[10–12]

Beta-cell function was also independently assessed from the 0 and 6 month oral glucose tolerance tests using the ratio of the 30 min incremental insulin and glucose concentration.[13]

Four cohorts of patients were selected according to duration of successful dietary therapy: those requiring additional treatment during the years 2 to 4, 5 to 7 and 8 to 10 years following diagnosis and those requiring no additional therapy for the full 10 years of follow-up. The cohorts were examined for characteristics at diagnosis and at 6 months following diagnosis, and trajectories of mean plasma glucose, obesity, HOMA % B and HOMA % S were plotted.

Duration of successful diet treatment was assessed using survival analysis, illustrated by Kaplan-Meier plots, and the significance of initial covariates was assessed by logrank tests for trend over tertiles of single covariates and stepwise Cox's proportional survival analysis for multiple covariates (BMDP Statistical Software, Cork, Ireland).

Results

Compliance and Survival

Of 432 patients originally recruited, 32 were lost to follow-up before the 6 month visit. Of the 400 patients followed for at least 6 months, a further 56 patients were lost to follow-up before either death of the patient or the completion of the 10-year study period. Of the remaining 344 patients, 233 survived and were followed up for the full 10 years of the study.

Progression of Diabetes

Patients were divided into four cohorts on the basis of the date of failure of diet therapy: the baseline and 6 month characteristics of the groups are presented in Table 1.

The progression of diabetes during the course of dietary therapy in the four groups is shown in Figure 1. The change in fasting plasma glucose in Figure 1(a) shows that the rate of rise was inversely related to the duration of successful dietary therapy. The mean rate of rise of plasma glucose in millimoles per year while on diet only for the four groups identified by the duration of dietary control varied from 0.2 mmol yr^{-1} in those who continued for 10 years to 1.5 mmol yr^{-1} in those who failed by 2–4 years (Figure 2). The weight profiles of the groups, expressed as the per cent of average body weight, is shown in Figure 1(b). Following the initial fall in weight in the first months of dietary therapy, weight was maintained in all groups while on diet therapy alone. Change of beta-cell function, HOMA % B, is shown in Figure 1(c). Data are only available for the first 6 years of follow-up, but the pattern of fall mirrors closely the rise in fasting plasma glucose seen in Figure 1(a). There was no difference in insulin sensitivity, assessed by HOMA % S, in any of the groups at 6 months from diagnosis, and no change during the further course of dietary therapy (Figure 1(d)).

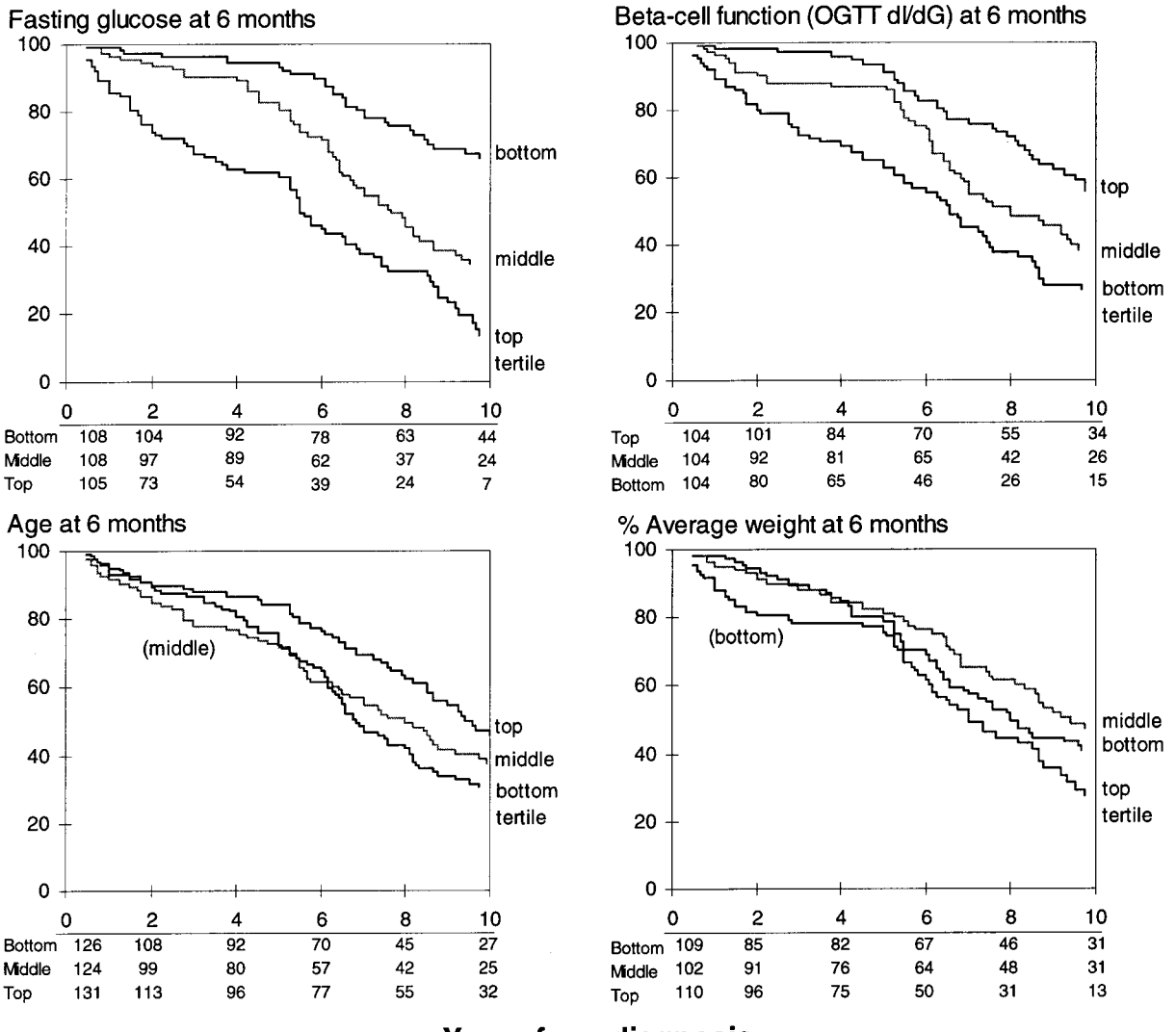

Figure 3. Progression of failure of dietary therapy by condition after the first 6 months (fasting glucose, beta-cell function, age, % average weight). Kaplan-Meier curves for tertiles of characteristics assessed at the 6-month visit. The lines represent the cumulative percentage of each group which remained on diet therapy only. Beneath each plot the numbers of evaluable subjects at risk of additional treatment is indicated at 6 months and for every 2 years after diagnosis for each tertile

Failure of Dietary Therapy

First 6 months

Of the 420 patients seen subsequent to the recruitment visit, 19 received primary insulin treatment and 5 primary tablet therapy before the 6 month review; 377 patients were on diet therapy at the 6 month review.

Beyond 6 months

Of patients on diet therapy at 6 months, insulin therapy was added in 35 and oral hypoglycaemic therapy was added in 149. Eighteen of these 149 were subsequently converted to insulin therapy. The median successful duration of diet therapy alone was 98 months. Figure 3 shows the Kaplan-Meier curves for continuation on diet therapy alone for tertiles of various characteristics assessed 6 months after diagnosis. Successful continuation on diet therapy was significantly associated with trend across tertiles for lower fasting plasma glucose ($p < 0.0001$), higher beta-cell function assessed by the 6 month OGTT ($p < 0.0001$) and increasing age ($p < 0.01$). Increased body weight at diagnosis was associated with longer continuation of diet therapy alone, but body weight at 6 months, after the initial fall due to institution of diet therapy was not associated with continuation on diet alone. Cox's proportional hazard analysis, using stepwise regression, identifies lower fasting plasma glucose (at diagnosis or at 6 months), higher beta-cell function (assessed by the oral glucose tolerance test either at diagnosis or at 6 months), lower age and per cent average weight at diagnosis (all $p < 0.001$), with increased duration of diet therapy alone.

Discussion

The present analysis of the complete data from the Belfast prospective study of diet treatment of Type 2

diabetes confirms the interim analysis of the first phase of the study in showing that patients continuing on diet alone for the first 10 years after diagnosis have a small but progressive rise in fasting plasma glucose, which is associated with an equally progressive fall in beta-cell function, but not with a change in either obesity or insulin sensitivity. In addition, it demonstrates that failure of diet therapy within the first 10 years is associated with higher rates of glucose rise and beta-cell decline, and that this failure of dietary therapy occurs earlier with higher initial glucose concentration, lower initial beta-cell function, lower age, and, for subjects maintained on diet therapy alone for at least 6 months, greater obesity.

The initial response to dietary restriction in newly presenting Type 2 diabetic patients is to improve insulin secretory capacity, but not to improve insulin sensitivity.[2,14,15] The longer term observation of the natural history of Type 2 diabetes on dietary therapy alone is confounded by the need for additional therapy in many patients. Sulphonylureas improve beta-cell function but are associated with weight gain, metformin increases insulin sensitivity, while insulin treatment makes the determination of both beta-cell function and insulin sensitivity problematical, as well as being associated with weight gain.

The Belfast prospective study applied uniform treatment criteria throughout the 10-year follow-up period. The relatively high threshold for the introduction of additional therapy was chosen in the light of concern about the possibility of adverse effects on cardiovascular disease reported for tolbutamide and phenformin by the UGDP intervention study. These thresholds, however, allow the examination of the course of the disease over a relatively long period on diet therapy alone. One aspect of the success of the dietary intervention is witnessed by the stability of weight in all groups, irrespective of the timing of the need for additional therapy.

The HOMA analysis of the first 6 years of follow-up of Phase 1 of the study was limited to those subjects who did not require additional therapy during the whole of this period.[6] Though these subjects represented the majority of subjects (131/182 subjects followed through-out this period), they also represented a group of diet therapy 'survivors'. The analysis of the first 6 years' data from the UKPDS, which examines the progression of the disease in randomly allocated treatment groups, similarly excluded patients who required additional therapy during the course of follow-up.[16] This was necessary to avoid the unequal representation of subjects with different durations of monotherapy in the group mean data, which, over a 6-year period would be a significant factor.

The current analysis approaches this problem, over a longer follow-up period, by considering cohorts of patients selected by treatment outcome, grouping patients requiring additional therapy in three separate blocks of 3 years, from 1 to 10 years following diagnosis, in addition to those patients who remained on diet treatment alone for the duration of the study. In this way, inequality of follow-up was reduced, if not abolished, within the groups. This allows the examination of factors associated with different rates of progression of the disease. In addition, the application of survival analysis to dietary therapy, where therapy failure is defined as the need for additional measures for glycaemic control, allows determination of the influence of early features on the duration of diet as a single therapy.

Early studies on the phenomenon of secondary failure to sulphonylurea therapy had suggested that poor primary selection of patients and inadequate dietary adherence were more important than inadequate dosage or developing drug resistance.[17,18] Type 2 diabetic patients are usually overweight and insulin resistant at diagnosis, but these predisposing factors do not change, given intensive dietary management, once the condition has been diagnosed and an initial weight loss due to restricted energy intake achieved. The progressive nature of the disease is rather due to the steady decline in beta-cell function, and it is the rate of this decline which determines the rate of failure of diet therapy. Preliminary data from the UKPDS demonstrate that additional therapy, either with oral hypoglycaemic agents or with insulin can produce a temporary improvement in plasma glucose, but do not affect the underlying and progressive beta-cell failure.[16] The present data cannot determine the degree to which beta-cell decline is exacerbated by hyperglycaemia, but the UKPDS data do not suggest that the rate of this decline is slowed by lowering glucose concentrations either by increasing endogenous insulin secretion with sulphonylureas or by reducing it with metformin or exogenous insulin.

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